Results for review of data about "suicides" in 1991 report

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A. Placebo controlled trials

1. Identify all placebo-controlled trials used in original NDA, including paroxetine and placebo data from three-arm trials. Studies PAR-04 and PAR-014 will be excluded by virtue of their design (PAR-04 is an extension of PAR-03, and encompasses some element of crossover of treatments between the two studies; PAR-014 is described as a placebo-controlled trial in the study title, but is more accurately considered as uncontrolled). Appendix A lists all studies contributing to this analysis, while applicable suicides are identified in Appendix B.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. Only the on-therapy phase will be included for patients continuing into an extension phase. Events occurring during an extension phase are captured in section C analysis. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. The hypothesis of no association between treatment and incidence of "suicide" will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
8. The number of suicide patients relative to PYE (incidence density) will be analysed using SAS® PROC GENMOD.
9. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
10. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine	Placebo	P-value
n/N (%)	0/921 (0.0%)	0/554 (0.0%)	#
PYE	108	51	
n/PYE (rate relative to exposure)	0.00	0.00	#

† in both cases above, n refers to the number of patients with the event

p-values are not obtainable from analysis of zero frequencies

Two patients (7119 009 and 7119 062) have been excluded from this analysis because their suicides occurred pre-treatment.

B. Active control trials

1. Identify all active-controlled trials used in original NDA, including paroxetine and active control data from three-arm trials. Study PAR-04 will be excluded by virtue of its design (PAR-04 is an extension of PAR-03, and encompasses some element of crossover of treatments between the two studies). Appendix A lists all studies contributing to this analysis, while applicable suicides are identified in Appendix B.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. Only the on-therapy phase will be included for patients continuing into an extension phase. Events occurring during an extension phase are captured in section C analysis. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. The hypothesis of no association between treatment and incidence of "suicide" will be tested using Fisher's exact test (two-tailed). Statistical significance will be assessed at the 5% level.
8. The number of suicide patients relative to PYE (incidence density) will be analysed using SAS PROC GENMOD.
9. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
10. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine	Active Control	P-value
n/N (%)	3/1096 (0.3%)	2/1063 (0.2%)	>0.999
PYE	136	120	
n/PYE (rate relative to exposure)	0.022	0.017	0.7588

† in both cases above, n refers to the number of patients with the event

An active control patient (237I 054) has been excluded from the count of events in this table because the event occurred 31 days post treatment.

An active control patient (6 67 002) who had a missing onset date for the adverse event "Suicide" has been included in the above analysis.

A paroxetine patient (1 13 126) has been excluded from the count of events in this table because the event occurred during the open label part of the study.
Two patients (7119 009 and 7119 062) have been excluded from this analysis because their suicides occurred pre-treatment.

C. All Paroxetine Data

1. Include data from all studies, both controlled and uncontrolled, including extension phases. Appendix A lists all studies contributing to this analysis, while applicable suicides are identified in Appendix B.
2. Confirm denominators for the subset of patients defined by point 1.
3. Confirm list of PIDs with events that were included in the 1991 FDA submission.
4. Exclude events outside the "On-Therapy plus 30 Days Post Therapy" window. (Note: on this basis events occurring during placebo run-in phases are excluded.)
5. Identify by footnote any patients excluded through point 4, if any, that were part of the list of patients with events in the 1991 FDA submission.
6. Calculate PYE for all patients, and calculate rate of patients with event relative to exposure. Exposure is calculated only for the period on-therapy, i.e. the 30-day post-therapy window is not used in calculating exposure.
7. Refer back to original Oracle tables, e.g. paroxetine_uspat.st@usarc7.
8. Provide a cell index listing patients with the event in both treatment groups.

	Paroxetine
n/N (%)	5/2963 (0.2%)
PYE	1008
n/PYE (rate relative to exposure)	0.005

† in both cases above, n refers to the number of patients with the event

Appendix A Study Population

Protocol Title	Section A	Section B	Section C
STUDY 001	X		X
STUDY 002	X		X
STUDY 003	X	X	X
STUDY 004			X
STUDY 005			X
STUDY 006		X	X
STUDY 007	X	X	X
STUDY 009	X		X
MDUK04 LAVIN		X	X
MDUK05 CORELESS			X
MDUK06 NAYLOR	X		X
MDUK07 SILVERSTONE	X	X	X
MDUK09 EDWARDS	X		X
MDUK12 TRIMBLE	X	X	X
MDUK13 WADE		X	X
MDUK14 TYRER			X
MDUK20 AKHTAR		X	X
MDUK22 CARLE/PENDER		X	X
MDUK24 SHANKS			X
MDUK25 ECCLESTONE		X	X
MDUK26 DORMAN		X	X
MDUK27 PEET/GHADVI		X	X
MDUK28 BRAY		X	X
MDUK29 SUD		X	X
MDUK30 SHUR		X	X
MDUK32 BEAUMONT		X	X
MDUK34 TRIMBLE			X
MDUK35 TOONE		X	X
MDUK37 MC			X
MDUK38 CHAKRAVARTI		X	X
MDUK40 GHOSE			X

MDUK41 WADE			X
MDUK42 WADE			X
MDUK43 WINSLOW		X	X

Protocol Title	Section A	Section B	Section C
MDUK44 RAO/SINGH			X
MDUK46 ADDALA		X	X
MDUK49 HUTCHINSON		X	X
STUDY 011		X	X
MDUK12A TRIMBLE			X
MDUK14B TYRER			X
MDUK17A CROME			X
MDUK17C CROME			X
MDUK28A BRAY		X	X
AUSTRIAN MC OPEN			X
MDA2 HEBENSTREIT			X
MDA3 HEBENSTREIT			X
MDA4 HEBENSTREIT			X
BELGIUM MC OPEN			X
BELGIUM M/C COMP		X	X
BELGIUM MC OPEN			X
FRENCH M/C COMP		X	X
MDF 1727 M/C COMP		X	X
MDF 1728 COMP		X	X
MDF 1729,1730,1731			X
GERMAN MC COMP		X	X
MDCH 1/2 MC OPEN			X
MDINT03 GAGIANO COMP		X	X
MDINT02 GAGIANO OPEN			X
HP/82/47A VERVARCKE		X	X
HP/82/64A GOFFAUX		X	X
HP/82/65A PRIEST			X
HP/83/67 MARGO		X	X
HP/81/74 LAXENAIRE		X	X

HP/81/85A VARACKX-HAENEN		X	X
HP/81/126A FELDMAN			X
HP/82/134 JAUHAR		X	X
HP/81/148 RICHOU		X	X
HP/81/162A BATTEGAY		X	X

Protocol Title	Section A	Section B	Section C
HP/81/164A GAIND			X
C1101 BORUP P42			X
C1102 SKAUSIG P6			X
DFG 119 DUAG P30		X	X
DFG121 THOMSEN P46			X
DFG122 VANGTORP P47			X
DFG 123 P31		X	X
DFG 124 P32		X	X
DFG126 PAUSER P46			X
61201 L.LAURSEN P41		X	X

Appendix B Suicide Events

Treatment	Study Title	Patient No	Section A	Section B	Section C
PLACEBO RUN-IN	DFG 119 DUAG P30	7119 009			
PLACEBO RUN-IN	DFG 119 DUAG P30	7119 062			
ACTIVE	MDF 1727 M/C COMP	237I 054			
ACTIVE	HP/83/67 MARGO	6 67 002		X	
ACTIVE	DFG 124 P32	7124 023		X	
PAROXETINE	MDUK13 WADE	1 13 126			X
PAROXETINE	BELGIUM MC OPEN	2206 005			X
PAROXETINE	GERMAN MC COMP	2406 149		X	X
PAROXETINE	HP/82/47A VERVARCKE	6 47 003		X	X
PAROXETINE	DFG 124 P32	7124 012		X	X

Two placebo run-in patients (7119 009 and 7119 062) have been excluded from all analysis.

Active control patients do not contribute to section C analysis (All Paroxetine Data)

An active control patient (237I 054) has been excluded from the section B analysis because the event occurred 31 days post treatment.

A paroxetine patient (1 13 126) has been excluded from the section B analysis because the event occurred during the open label part of the study.

An active control patient (6 67 002) who had a missing onset date for the adverse event "Suicide" has been included in the section B analysis.